Exploring the Intertwined Roles of APOE and ABC Genes in the Cognitive Decline of Alzheimers

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***Abstract*—Alzheimer disease (AD)is one of the most common causes of dementia in individuals older than 60 years. Several susceptibility genes for AD have been reported earlier, but by far,the strongest genetic risk factor for late onset Alzheimer disease (LOAD) is apolipoprotein E (APOE) genotype, with the ε4 allele being an AD risk factor and the ε2 allele being protective. Therapeutic strategies based on APOE and APOE receptors should aim to target influencing APOE/Aβ interactions, APOE structure, APOE lipidation, LDLR receptor family member function, and signaling. This paper will explain the intertwined roles of ABCA1 and APOE in understanding the molecular and pathophysiological mechanisms of Alzheimers disease. It will extensively describe the normal and disease-related biology connecting APOE, APOE receptors in AD and provide novel insights into AD prognosis and treatment.**

***Key Words*—Alzheimers disease, ABC gene, APOE gene**

I. INTRODUCTION

Scientists believe that many factors influence whenAlzheimer's disease begins and how it progresses. The more they study this devastating disease, the more they realize that genes play an important role. Research conducted and funded by the National Institute on Aging (NIA) at the National Institutes of Health (NIH) and othersis advancing our understanding of Alzheimer's disease genetics[1].

II. BACKGROUND

The Genetics of Disease

Some diseases are caused by a genetic mutation, or permanent change in one or more specific genes. If a person inherits from a parent a genetic mutation that causes a certain disease, then he or she will usually get the disease.[2] Sickle cell anemia, cystic fibrosis, and earlyonset familial Alzheimer's disease are examples of inherited geneticdisorders. In other diseases, a genetic variant may occur. A single gene can have many variants. [3]Sometimes, this difference in a gene can cause a disease directly. More often, a variant plays a role in increasing or decreasing a person's risk of developing a disease or condition. When a genetic variant increasesdisease risk but does not directly cause a disease, it is called a genetic risk factor. Identifying genetic variants may help researchers find the most effective ways to treat or prevent diseases such as Alzheimer's in an individual. This approach, called precision medicine, takes into account individual variability in genes, environment, and lifestyle for each person[4].

III. MAIN CHAPTER

What Are DNA, Chromosomes, and Genes?

The nucleus of almost every human cell contains a "blueprint"that carries the instructions acell needs to do its job. The blueprint is made up of DNA (deoxyribonucleic acid), which is present in long strands that would stretch to nearly 6 feet in length if attached end to end.[5] The DNA is packed tightly together with proteins into compact structures called chromosomes. Normally, each cell has 46 chromosomes in 23 pairs, which are inherited equally from a person's biological parents. The DNA in nearly all cells of an individual is identical. Each chromosome contains many thousands of segments, called genes. People inherit two copies of each gene from their parents, except for genes on the X and Y chromosomes, which, among other functions, determine a person's sex. [6]The genes "instruct" the cell to make unique proteins that, in turn, dictate the types of cells made. Genes also direct almost every aspect of a cell's construction, operation, and repair. Even slight changes in a gene can produce a protein that functions abnormally.[7]

Alzheimer's Disease Genetics

Alzheimer's disease is an irreversible, progressive brain disease. It is characterized by the development of amyloid plaques and neurofibrillary, or tau, tangles; the loss of connections between nerve cells (neurons) in the brain; and the death of these nerve cells. There are two types of Alzheimer's— early-onset and late-onset. Both types have a genetic component. which may lead to disease. Other changes in genes may increase or decrease a person's risk of developing a particular disease[8].

Early-Onset Alzheimer's Disease

Early-onset Alzheimer's disease occurs in people age 30 to 60 and represents less than 5 percent of all people

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with Alzheimer's. [9]Most cases are caused by an inherited change in one of three genes, resulting in a type known as early-onset familial Alzheimer's disease, or FAD. For others, the disease appears to develop without any specific, known cause. A child whose biological mother or father carries a genetic mutation for early-onset FAD has a 50/50 chance of inheriting that mutation. If the mutation is in fact inherited, the child has a very strong probability of developing early-onset FAD[10]. Early-onset FAD is caused by any one of a number of different singlegene mutations on chromosomes 21, 14, and 1. Each of these mutations causes abnormal proteins to be formed. Mutations on chromosome 21 cause the formation of abnormal amyloid precursor protein (APP). A mutation on chromosome 14 causes abnormal presenilin 1 to be made, and a mutation on chromosome 1 leads to abnormal presenilin 2.[11] Each of these mutations plays a role in the breakdown of APP, a protein whose precise function is not yet fully understood. This breakdown is part of a process that generates harmful forms of amyloid plaques, a hallmark of Alzheimer's disease. Critical research findings about early-onset Alzheimer's have helped identify key steps in the formation of brain abnormalities typical of the more common late-onset form of Alzheimer's. Genetics studies have helped explain why the disease develops in people at various ages. NIA-supported scientists are continuing research into early-onset disease through the Dominantly Inherited Alzheimer Network (DIAN), an international partnership to study families with early-onset FAD. By observing the Alzheimer's-related brain changes that occur in these families long before symptoms of memory loss or cognitive issues appear, scientists hope to gain insight into how and why the disease develops in both its early- and late-onset forms. In addition, an NIA-supported clinical trial in Colombia, South America, is testing the effectiveness of an amyloid clearing drug in symptom-free volunteers at high risk of developing early onsetFAD.

Late-Onset Alzheimer's Disease

Most people with Alzheimer's have the late-onset form of the disease, in which symptoms become apparent in the mid-60s and later. The causes of late-onset Alzheimer's are not yet completely understood, but they likely include a combination of genetic, environmental, and lifestyle factors that affect a person's risk for developing the disease.[12] Researchers have not found a specific gene that directly causes the late onset form of the disease. However, one genetic risk factor—having one form of the apolipoprotein E*(APOE) gene* on chromosome 19—does increase a person's risk. [13]

APOE comes in several different forms, or *alleles*: *APOE e2* is relatively rare and may provide some protection against the disease. If Alzheimer's disease occurs in a person with this allele, it usually develops later in life than it would in someone with the APOE e4 gene. *APOE e3*, the most common allele, is believed to play a neutral role in the disease—neither decreasing nor increasing risk. *APOE e4* increases risk for Alzheimer's disease and is also associated with an earlier age of disease onset. A person has zero, one, or two APOE e4 alleles. Having more APOE e4 alleles increases the risk of developing Alzheimer's. APOE e4 is called a risk-factor gene because it increases a person's risk of developing the disease. However, inheriting an APOE e4 allele does not mean that a person will definitely Develop Alzheimer's. Some people with an APOE e4 allele never get the disease, and others who develop Alzheimer's do not have any APOE e4 alleles. Using a relatively new approach called *genome-wide association study (GWAS),* researchers have identified a number of regions of interest in the *genome* (an organism's complete set of DNA, including all of its genes) that may increase a person's risk for late-onset Alzheimer's to varying degrees. By 2015, they had confirmed 33 regions of interest in the Alzheimer's genome.[14] A method called whole genome sequencing determines the complete DNA sequence of a person's genome at a single time. Another method called whole exome sequencing looks at the parts of the genome that directly code for proteins. Using these two approaches, researchers can identify new genes that contribute to or protect against disease risk. Recent discoveries have led to new insights about biological pathways involved in Alzheimer's and may one day lead to effective interventions.

Genetic Testing

A blood test can identify which APOE alleles a person has, but results cannot predict who will or will not develop Alzheimer's disease. It is unlikely that genetic testing will ever be able to predict the disease with 100 percent accuracy, researchers believe, because too many other factors may influence its development and progression. Currently, APOE testing is used in research settings to identify study participants who may have an increased risk of developing Alzheimer's.[15] This knowledge helps scientists look for early brain changes in participants and compare the effectiveness of treatments for people with different APOE profiles. Most researchers believe that APOE testing is useful for studying Alzheimer's disease risk in large groups of people but not for determining any one person's risk. Genetic testing is used by researchers conducting clinical trials and by physicians to help diagnose early-onset Alzheimer's disease. However, genetic testing is not otherwise recommended. Several susceptibility genes for AD have been reported earlier, but by far, the strongest genetic risk factor for late onset Alzheimer disease (LOAD) is apolipoprotein E (APOE) genotype, with the ε4 allele being an AD risk factor and the ε2 allele being protective. In the central nervous system, APOE is present in high-density lipoproteins. It is produced by glial cells and interacts with several low-density lipoprotein receptors (LDLR). There are many mechanisms by which the APOE isoform may influence CNS function and risk for AD. These differential

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effects are influenced by the ability of APOE to affect Aβ aggregation and clearance in the brain. Other mechanisms like cell signaling, synaptic plasticity, lipid transport and metabolism, and neuro-inflammation also play a likely role. This includes coordinated effects on APOE receptors, including LDLRs, APOER2, very low-density lipoprotein receptors (VLDLRs), and lipoprotein receptor-related protein 1 (LRP1). These mechanisms appear to influence both the CNS effects of APOE as well as Aβ metabolism and toxicity. The ATP-binding cassette, sub-family A, member 1 gene (ABCA1) is also a potential candidate risk gene for late onset Alzheimer's disease (LOAD) as a consequence of its role in cholesterol transport and metabolism. In mouse models, ABCA1 has been shown to enable the clearance of amyloid-β peptide from the brain, through its role in apolipoprotein (APOE) lipidation. Genome wide association studies (GWAS) and next generation sequencing of pooled DNA have indicated rare variants in ABCA1 that influence plasma high-density lipoprotein cholesterol levels. New researches have found a significantly higher proportion of sporadic non-synonymous variants in control individuals as compared to AD cases,thereby suggestive of a protective effect. Therapeutic strategies based on APOE and APOE receptors should aim to target influencing APOE/Aβ interactions, APOE structure, APOE lipidation, LDLR receptor family member function, and signaling. [16]

IV. FUTURE RESEARCH DIRECTIONS

Discovering all that we can about Alzheimer's disease genetic risk and protective factors is an important area of research. Further research can be focused solving the following

- What makes the disease process begin?
- Why do some people with memory and other thinking problems develop Alzheimer's while others do not?
- Determine how genetic risk and protective factors may interact with other genes and lifestyle or environmental factors to affect Alzheimer's risk in any one person.
- Identify people who are at high risk for developing Alzheimer's so they can benefit from new interventions
- and treatments as soon as possible.
- Focus on new prevention and treatment approaches.

V. CONCLUSION

Scientists have long thought that genetic and environmental factors interact to influence a person's biological makeup, including the predisposition to different diseases. More recently, they have discovered the biological mechanisms for those interactions. The expression of genes (when particular genes are "switched" on or off) can be affected—positively and negatively—by environmental factors at any time in life. These factors include exercise, diet, chemicals, or smoking, to which an individual may be exposed, even in the womb. Epigenetics is an emerging science focused on how and when particular genes are turned on or off. Diet and exposure to chemicals in the environment, among other factors, can alter a cell's DNA in ways that affect the activity of genes. That can make people more or less susceptible to developing a disease. There is emerging evidence that epigenetic mechanisms contribute to Alzheimer's disease. Epigenetic changes, whether protective, benign, or harmful, may help explain, for example, why one family member develops the disease and another does not. Scientists are learning more about Alzheimer's-related epigenetics, with the hope of developing individualized treatments based on epigenetic markers and their function.

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